IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Buechler et al.

Title: MARKERS FOR DIFFERENTIAL DIAGNOSIS AND METHODS OF USE THEREOF

Appl. No.: 10/603,891

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Examiner: Unsu Jung

Art Unit: 1641

Confirmation Number 4895

DECLARATION OF JOSEPH ANDERBERG UNDER 37 C.F.R §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Joseph Anderberg, hereby declare as follows:

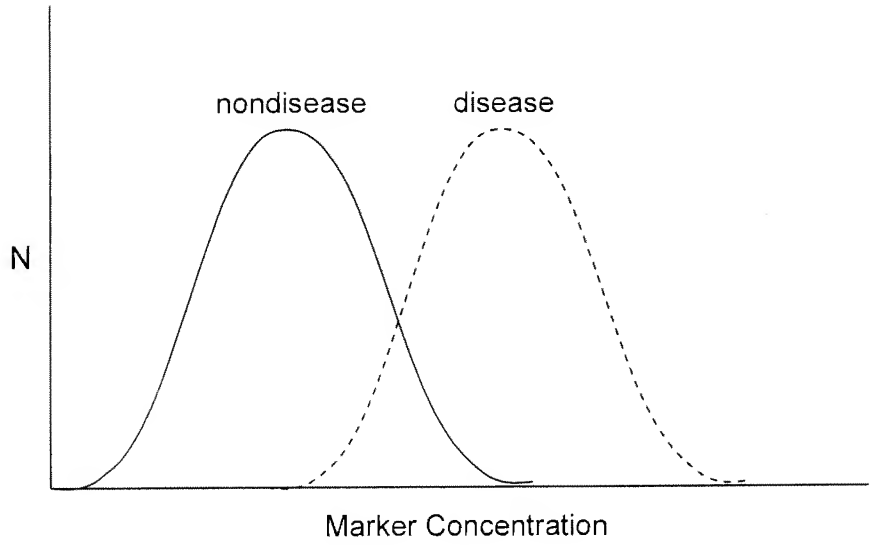
1. I received a B.S. in physics from Harvey Mudd College in 1983, and a Ph.D. in experimental condensed matter physics from the University of California, San Diego in 1992. I am currently Senior Director of Quantitative Research at Biosite Incorporated, the Assignee of the above-referenced patent application. I have expertise in data analysis algorithms, particularly as applied to diagnostic assays. I am named as an inventor on four issued U.S. patents and five families of U.S. patent applications. In particular, I am named as an inventor of the above-identified patent application.

2. I am aware that the patent examiner has cited Zweig and Campbell, *Clin. Chem.* 39: 561-77 (1993) (hereinafter referred to as Zweig *et al.*) in an obviousness rejection for its teachings regarding the use of ROC curves. The Examiner characterizes Zweig *et al.* as follows:

> Zweig et al. teaches receiver-operating characteristics (ROC) plots as an evaluation tool in clinical performance of laboratory tests (Abstract). The use of ROC plots has many advantages (p568, left column, Advantages of ROC Plots). It is a comprehensive representation of pure accuracy, i.e. discriminating ability, over the entire range of the test. It does not require selection of a particular decision threshold because the whole spectrum of possible decision thresholds is included. It is independent of prevalence: No care need be taken to obtain samples with representative prevalence. It provides a direct visual comparison between tests on a common scale, whereas both dot diagrams and frequency histograms require different plots if the scales differ. It requires no grouping or binning of data, as do frequency histograms. Its specificity and sensitivity are readily accessible, in contrast to dot diagrams and frequency histograms.

3. I have been asked whether the Examiner's characterization of Zweig *et al.*, as allegedly teaching the use of biomarkers for characterizing the disease state of an individual subject without the use of a decision threshold, is correct. For the following reasons, I conclude that the Examiner's characterization of Zweig *et al.* is incorrect. Instead, Zweig *et al.* describes the use of Receiver-Operator Characteristic ("ROC") analysis to evaluate the ability of the test to discriminate a diseased population from a nondiseased population). This use of ROC analysis to evaluate the performance of a laboratory test is well established in the art, but is completely unrelated to characterizing the disease state of an individual subject.

4. When evaluating a marker of interest for its ability to distinguish disease from nondisease, one typically measures the marker in these two populations. Typically, the populations will exhibit some overlap in marker values in the manner shown in the following drawing:



5. Any particular marker concentration chosen as a diagnostic threshold will include some number of either false negatives (if the threshold is within the diseased population, but outside the overlap region), false positives (if the threshold is within the nondiseased population, but outside the overlap region), or both false negatives and false positives (if the threshold is within the overlap region). Thus, the traditional selection and use of a diagnostic threshold to evaluate the disease state of an individual subject necessarily involves a tradeoff between sensitivity and specificity. This is discussed, for example, in Zweig *et al.*, page 563, right column, section entitled "Diagnostic Sensitivity/Specificity.

6. As is also discussed in Zweig *et al.*, ROC analysis can be used to determine the clinical performance of such a test, which, as noted in the first paragraph of Zweig *et al.*, refers to "the ability to correctly classify subjects into clinically relevant subgroups." As shown in Fig. 4 of Zweig *et al.*, in ROC analysis, one plots the sensitivity (the "true positives") against 1-specificity (the "true negatives") in the two populations. As noted in the first incomplete paragraph on page 565 of Zweig *et al.*, each point on the ROC plot represents a sensitivity/specificity pair corresponding to a particular threshold concentration. A theoretical "perfect test" curve would pass through the upper left corner of the ROC plot; a theoretical test that cannot discriminate between the two groups would produce a 45° line extending from the lower left corner of the ROC plot.

7. An actual test will typically fall somewhere between the two extremes of "perfect" and "nondiagnostic." ROC analysis can be used to provide a quantitative value

concerning the ability of the test to distinguish disease from nondisease. For example, as discussed on page 568, right column, of Zweig *et al.*, an area under the ROC curve can be calculated. A perfect test will exhibit a ROC area of 1.0, and a nondiagnostic test will exhibit a ROC area of 0.5. Other measures useful to evaluate the clinical performance of such a test are also discussed in Zweig *et al.*

8. Zweig *et al.* is quite correct that ROC analysis is used in evaluating the ability of a particular test to discriminate a diseased population from a nondiseased population. But using a test to evaluate the disease state of an individual requires an entirely different type of analysis. ROC analysis can be used to help *guide the selection of a diagnostic threshold*, as discussed beginning on page 571, right column, of Zweig *et al.*, and such a threshold can then be used to evaluate individuals. And, in fact, Zweig *et al.* states that "to use the test for **patient management**, a decision threshold **must** be selected." Page 572, first incomplete paragraph, emphasis added. Thus, contrary to the Examiner's belief, Zweig *et al.* not only fails to describe the use of markers for characterizing individual subject's disease status without comparing markers to a predetermined threshold, it actually teaches that one cannot do so.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the captioned patent application or any patent issued therefrom.

1/10/07
Date

Joseph Anderberg